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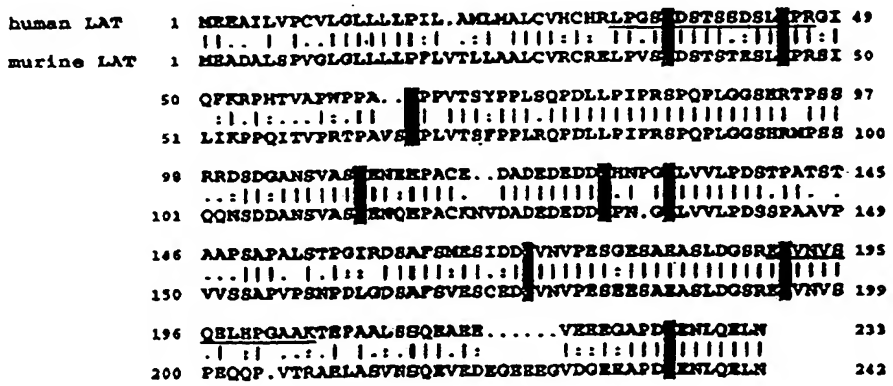
(54) Title: THE PROTEIN TYROSINE KINASE SUBSTRATE LAT AND ITS USE IN THE IDENTIFICATION OF (ANT)AGONISTS OF THE KINASE



Human (1-233) and Murine LAT Amino Acid Sequence (1-242)

(57) Abstract

The invention generally relates to compositions and methods for identifying and testing tyrosine kinase signaling pathway agonists and antagonists, and more particularly, methods and compositions for screening compounds and identifying compounds that will modulate the interaction of protein tyrosine kinase substrates with their intracellular ligands, as well as between their intracellular ligands and other members of the signaling pathway.

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CLAIMS

We claim:

1. An isolated polypeptide comprising at least a portion of the amino acid sequence of SEQ ID NO:4.

2. The isolated polypeptide of Claim 1, wherein said portion comprises a region comprising at least one tyrosine.

3. The isolated polypeptide of Claim 1, wherein said portion comprises a region defined by amino acids 28 to 233.

4. A purified antibody which binds specifically to a polypeptide comprising at least a portion of the amino acid sequence of SEQ ID NO:4.

5. The purified antibody of Claim 4, wherein said antibody is a polyclonal antibody.

6. The purified antibody of Claim 4, wherein said antibody is a monoclonal antibody.

7. An isolated polynucleotide encoding the polypeptide comprising the sequence of SEQ ID NO:4.

8. The isolated polynucleotide of Claim 7, wherein said polynucleotide comprises the sequence of SEQ ID NO: 1

9. The isolated polynucleotide of Claim 7, wherein said polynucleotide is contained on a recombinant expression vector.

10. The polynucleotide sequence of Claim 9, wherein said expression vector containing said polynucleotide sequence is contained within a host cell.

11. A polynucleotide sequence that hybridizes under stringent conditions to the nucleic acid sequence of SEQ ID NO:1.

12. A method of screening a compound, said method comprising:

a) providing, in any order:

i) a peptide comprising at least a portion of the amino acid sequence set forth in SEQ ID NO:4, wherein said portion is capable of binding to a LAT binding ligand;

ii) a LAT binding ligand; and

iii) one or more compounds for screening;

b) mixing, in any order, said peptide, said LAT binding ligand and said one or more compound; and

c) measuring the extent of binding of said peptide to said LAT binding ligand.

13. The method of Claim 12, wherein said LAT binding ligand comprises a tyrosine kinase.

14. The method of Claim 13, wherein said kinase comprises ZAP-70 kinase.

15. The method of Claim 13, wherein said kinase comprises Syk kinase.

16. The method of Claim 12, wherein said peptide is part of a fusion protein.

17. A method for detecting the presence of a portion of the polypeptide having the amino acid sequence set forth in SEQ ID NO:4, said method comprising the steps of:

a) providing in any order:

i) an antibody capable of reacting with a portion of the polypeptide having the sequence set forth in SEQ ID NO:4; and

ii) a sample suspected of containing at least a portion of the polypeptide having the sequence set forth in SEQ ID NO: 4;

b) combining said antibody and said sample under conditions such that a complex is formed between said antibody and said portion of said polynucleotide; and

c) detecting said complex.

18. The method of Claim 17, wherein said antibody is a polyclonal antibody.

19. The method of Claim 17, wherein said antibody is a monoclonal antibody.

20. The method of Claim 17, wherein said sample comprises lymphocytes.

21. A method for detecting the presence of polynucleotide sequences encoding at least a portion of LAT gene in a sample, said method comprising the steps of:

a) providing in any order:

i) a polynucleotide comprising a sequence that hybridizes under stringent conditions to the nucleic acid sequence of SEQ ID NO:1; and

ii) a sample suspected of containing nucleic acid comprising the sequence of SEQ ID NO:1;

b) combining said polynucleotide and said sample under conditions such that a hybridization complex is formed between said polynucleotide and said sample nucleic acid; and

c) detecting said hybridization complex.

22. The method of Claim 21, wherein said sample nucleic acid is RNA.

23. The method of Claim 21, wherein said sample nucleic acid is DNA.

24. The method of Claim 21, wherein said sample comprises lymphocytes.

25. The method of Claim 24, wherein said detected hybridization complex correlates with expression of the LAT gene in said lymphocytes.

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Human Vav Nucleotide Sequence (1-2757)

Figure 11A

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481 kacqmllrgt fyqgyrchrc rasahkeclg rvppcgrhgq dfpgtmkkdk lhrraqdkkr
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661 kynvevkhtv kimtaeglyr itekkafrgl telvefyqqn slkdcfksld ttlqfpfkep
721 ekrtisrpav gstkyfgtak arydfcardr selslkegdi ikilnkkgqq gwwrgeiygr
781 vgwfpanyve edyseyc

Human Vav Amino Acid Sequence (1-797)

Figure 11B

1 gaattccggg cccggatagc cggcggcggc ggcggcggcg gcggcggcgg cggccgggag
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Human Cbl Nucleotide Sequence (1-3090)

Figure 12A

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Human Cbl Amino Acid Sequence (1-896)

Figure 12B

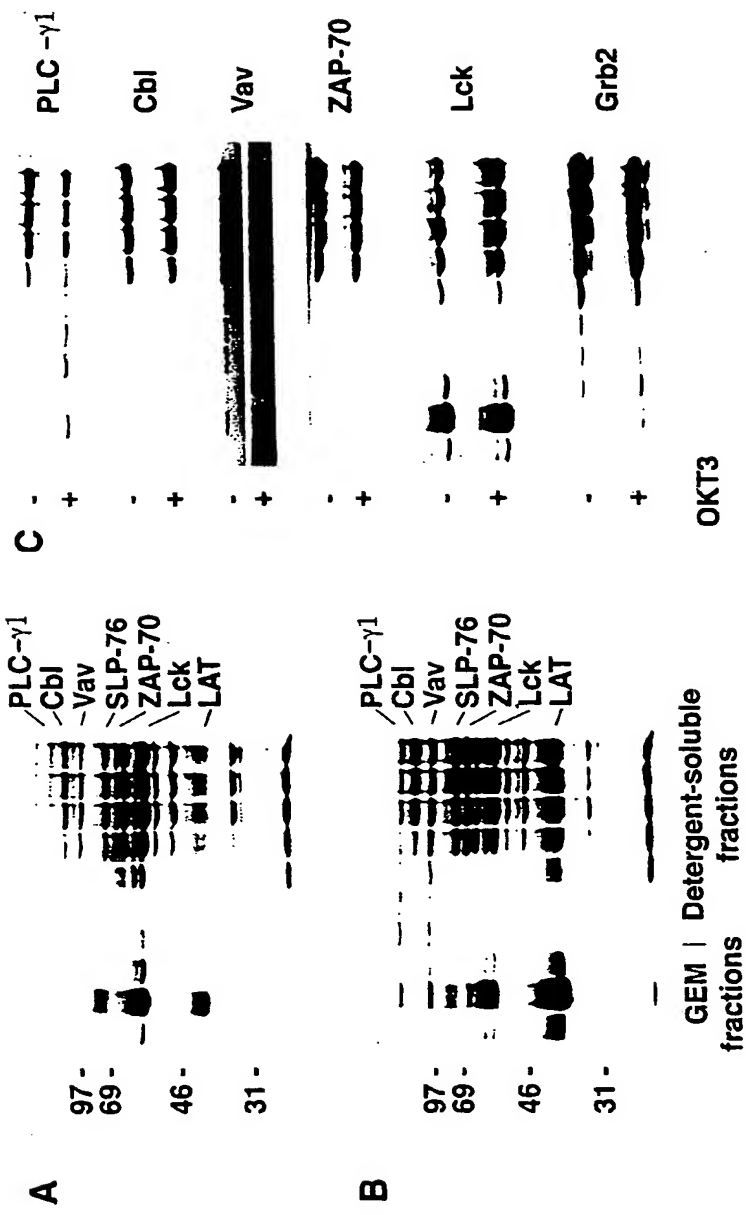

Fig. 13

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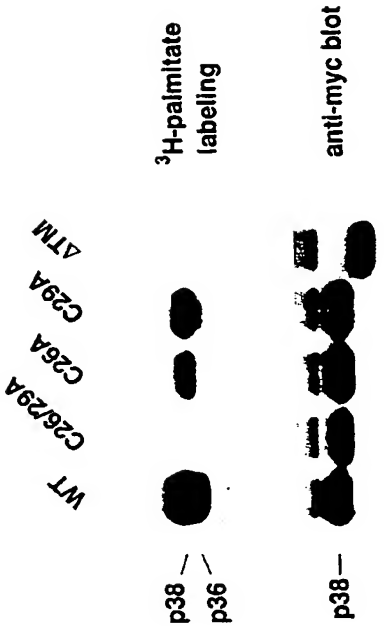

FIG. 14

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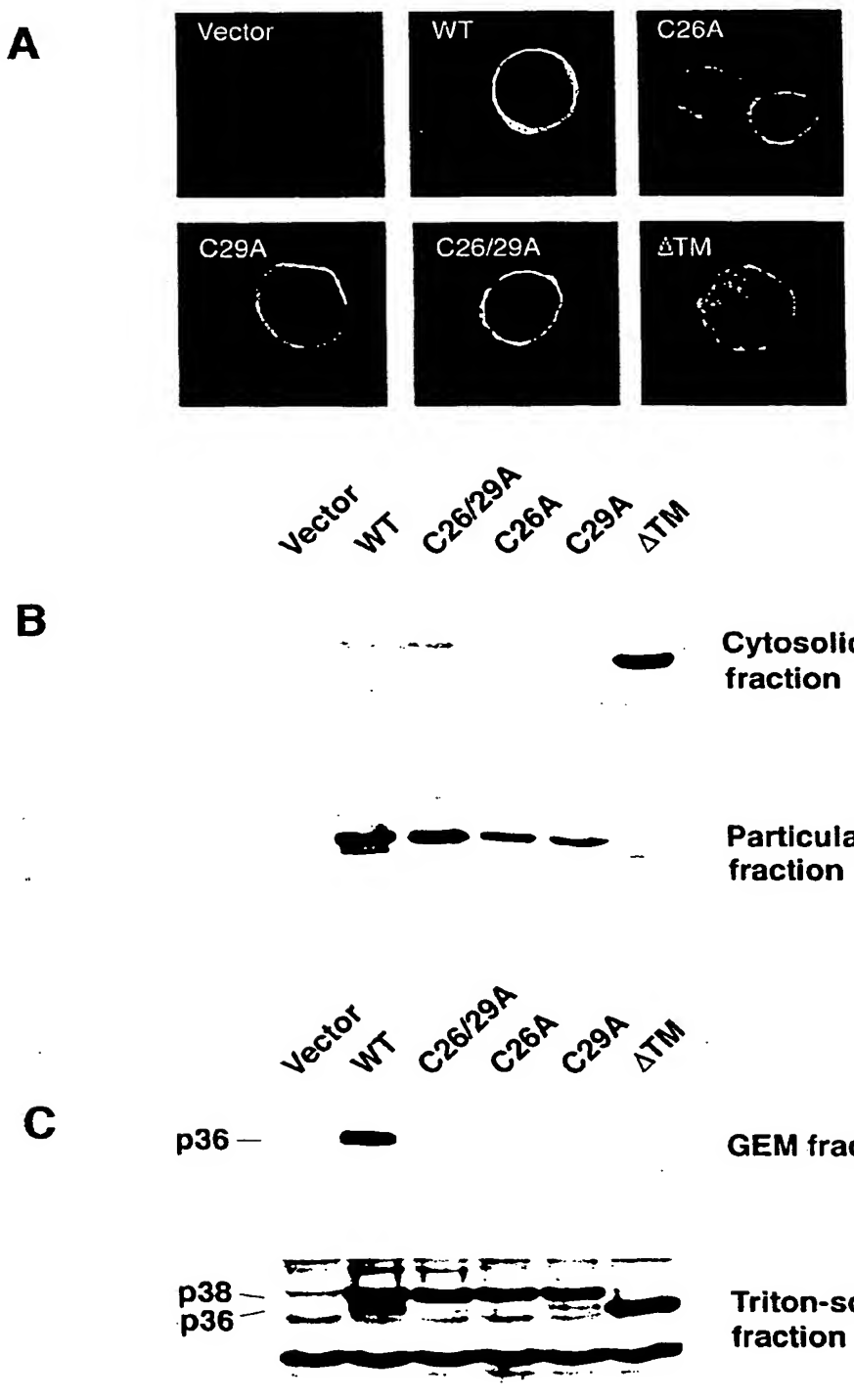

FIG. 15

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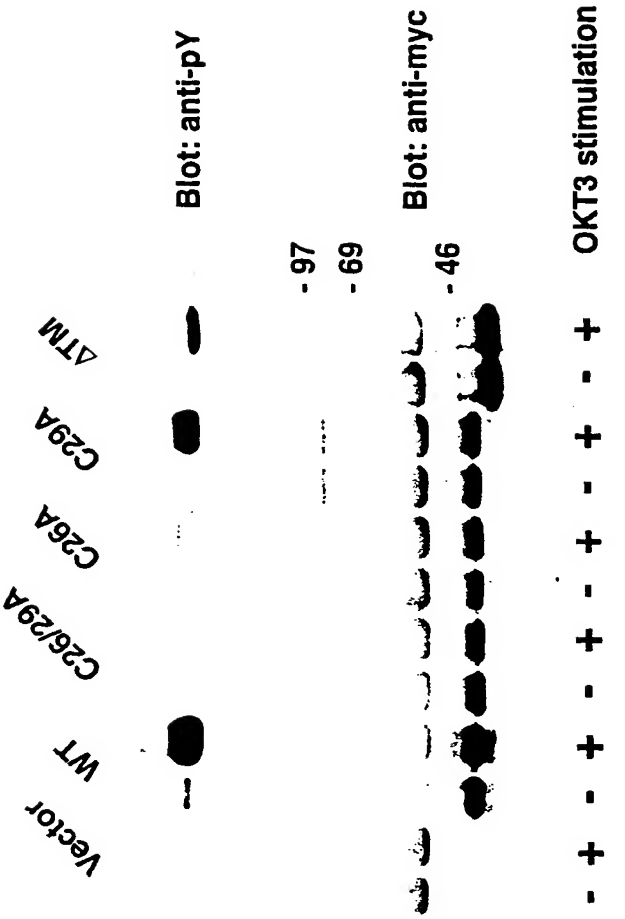

Fig. 16

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SEQUENCE LISTING

<110> Samelson, Lawrence E.
Zhang, Weiguo

<120> Compositions and Methods for Identifying and Testing Tyrosine Kinase Substrates and Their Agonists and Antagonists

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<212> DNA
<213> Mus musculus

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<212> PRT
<213> Homo sapiens

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Pro Gly Ser Tyr Asp Ser Thr Ser Ser Asp Ser Leu Tyr Pro Arg Gly
35 40 45

Ile Gln Phe Lys Arg Pro His Thr Val Ala Pro Trp Pro Pro Ala Tyr
50 55 60

Pro Pro Val Thr Ser Tyr Pro Pro Leu Ser Gln Pro Asp Leu Leu Pro
65 70 75 80

Ile Pro Arg Ser Pro Gln Pro Leu Gly Gly Ser His Arg Thr Pro Ser
85 90 95

Ser Arg Arg Asp Ser Asp Gly Ala Asn Ser Val Ala Ser Tyr Glu Asn
100 105 110

Glu Glu Pro Ala Cys Glu Asp Ala Asp Glu Asp Glu Asp Asp Tyr His
115 120 125

Asn Pro Gly Tyr Leu Val Val Leu Pro Asp Ser Thr Pro Ala Thr Ser
130 135 140

Thr Ala Ala Pro Ser Ala Pro Ala Leu Ser Thr Pro Gly Ile Arg Asp
145 150 155 160

Ser Ala Phe Ser Met Glu Ser Ile Asp Asp Tyr Val Asn Val Pro Glu
165 170 175

Ser Gly Glu Ser Ala Glu Ala Ser Leu Asp Gly Ser Arg Glu Tyr Val
180 185 190

Asn Val Ser Gln Glu Leu His Pro Gly Ala Ala Lys Thr Glu Pro Ala
195 200 205

Ala Leu Ser Ser Gln Glu Ala Glu Glu Val Glu Glu Glu Gly Ala Pro
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Asp Tyr Glu Asn Leu Gln Glu Leu Asn
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<212> DNA
<213> Murinae gen. sp.

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<212> DNA
<213> Homo sapiens

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<210> 7
<211> 617
<212> PRT
<213> Homo sapiens

<400> 7

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Arg Ala Glu Ala Glu Glu His Leu Lys Leu Ala Gly Met Ala Asp Gly
            20                  25                  30

Leu Phe Leu Leu Arg Gln Cys Leu Arg Ser Leu Gly Gly Tyr Val Leu
        35                  40                  45

Ser Leu Val Asp Asp Val Arg Phe His His Phe Pro Ile Glu Arg Gln
    50                  55                  60

Leu Asn Gly Thr Tyr Ala Ile Ala Gly Gly Lys Ala His Cys Gly Pro
65                  70                  75                  80

Ala Glu Leu Cys Gln Phe Tyr Ser Gln Asp Pro Asp Gly Leu Pro Cys
                85                  90                  95

Asn Leu Arg Asn Ala Cys Asn Arg Pro Pro Gly Leu Glu Pro Gln Pro
            100                 105                 110

Gly Val Phe Asp Cys Leu Arg Asp Ala Met Val Arg Asp Tyr Val Arg
        115                 120                 125

Gln Thr Trp Lys Leu Glu Gly Asp Ala Leu Glu Gln Ala Ile Ile Ser
    130                 135                 140

Gln Ala Pro Gln Val Glu Lys Leu Ile Ala Thr Thr Ala His Glu Arg
145                 150                 155                 160

Met Pro Trp Tyr His Ser Ser Leu Thr Arg Glu Glu Ala Glu Arg Lys
                165                 170                 175

Leu Tyr Ser Gly Gln Gln Thr Asp Gly Lys Phe Leu Leu Arg Pro Arg
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```
Lys Glu Gln Gly Thr Tyr Ala Leu Ser Leu Val Tyr Gly Lys Thr Val
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Tyr His Tyr Leu Ile Ser Gln Asp Lys Ala Gly Lys Tyr Cys Ile Pro
    210                 215                 220

Glu Gly Thr Lys Phe Asp Thr Leu Trp Gln Leu Val Glu Tyr Leu Lys
225                 230                 235                 240

Leu Lys Ala Asp Gly Leu Ile Tyr Arg Leu Lys Glu Val Cys Pro Asn
                245                 250                 255

Ser Ser Ala Ser Ala Ala Val Ala Ala Pro Thr Leu Pro Ala His Pro
            260                 265                 270

Ser Thr Phe Thr Gln Pro Gln Arg Arg Val Asp Thr Leu Asn Ser Asp
        275                 280                 285

Gly Tyr Thr Pro Glu Pro Ala Arg Leu Ala Ser Ser Thr Asp Lys Pro
    290                 295                 300

Arg Pro Met Pro Met Asp Thr Ser Val Tyr Glu Ser Pro Tyr Ser Asp
305                 310                 315                 320

Pro Glu Glu Leu Lys Asp Lys Lys Leu Phe Leu Lys Arg Glu Asn Leu
                325                 330                 335

Leu Val Ala Asp Ile Glu Leu Gly Cys Gly Asn Phe Gly Ser Val Arg
            340                 345                 350

Gln Gly Val Tyr Arg Met Arg Lys Lys Gln Ile Asp Val Ala Ile Lys
        355                 360                 365

Val Leu Lys Gln Gly Thr Glu Lys Ala Asp Lys Asp Glu Met Met Arg
    370                 375                 380

Glu Ala Gln Ile Met His Gln Leu Asp Asn Pro Tyr Ile Val Arg Leu
385                 390                 395                 400

Ile Gly Val Cys Gln Ala Glu Ala Leu Met Leu Val Met Glu Met Ala
                405                 410                 415

Gly Gly Gly Pro Leu His Lys Phe Leu Leu Gly Lys Lys Glu Ile Pro
            420                 425                 430

Val Ser Asn Val Ala Glu Leu Leu His Gln Val Ala Met Gly Met Lys
        435                 440                 445

Tyr Leu Glu Glu Lys Asn Phe Val His Arg Asp Leu Ala Ala Arg Asn
    450                 455                 460

Val Leu Leu Val Asn Arg His Tyr Ala Lys Ile Ser Asp Phe Gly Leu
465                 470                 475                 480

Ser Lys Ala Leu Gly Ala Asp Asp Ser Tyr Tyr Thr Ala Arg Ser Ala
                485                 490                 495

Gly Lys Trp Pro Leu Lys Trp Tyr Ala Pro Glu Cys Ile Asn Phe Arg
            500                 505                 510

Lys Phe Ser Ser Arg Ser Asp Val Trp Ser Tyr Gly Val Thr Met Trp
        515                 520                 525

Glu Ala Phe Ser Tyr Gly Gln Lys Pro Tyr Lys Lys Met Lys Gly Pro
    530                 535                 540

Glu Val Leu Asp Phe Ile Lys Gln Gly Lys Arg Met Glu Cys Pro Pro
545                 550                 555                 560
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```
Glu Cys Pro Pro Glu Met Tyr Ala Leu Met Ser Asp Cys Trp Ile Tyr
                565                 570                 575

Lys Trp Glu Asp Arg Pro Asp Phe Leu Thr Val Glu Gln Arg Met Arg
            580                 585                 590

Asn Tyr Tyr Tyr Ser Leu Ala Ser Arg Ala Glu Gly Pro Pro Gln Cys
        595                 600                 605

Glu Gln Val Ala Glu Ala Ala Cys Gly
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<210> 8
<211> 2541
<212> DNA
<213> Homo sapiens

<400> 8

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<210> 9
<211> 635
<212> PRT
<213> Homo sapiens

<400> 9

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            20                  25                  30

Gly Met Ser Asp Gly Leu Tyr Leu Leu Arg Gln Ser Arg Asn Tyr Leu
        35                  40                  45

Gly Gly Phe Ala Leu Ser Val Ala His Gly Arg Lys Ala His His Tyr
    50                  55                  60

Thr Ile Glu Arg Glu Leu Asn Gly Thr Tyr Ala Ile Ala Gly Gly Arg
65                  70                  75                  80

Thr His Ala Ser Pro Ala Asp Leu Cys His Tyr His Ser Gln Glu Ser
                85                  90                  95

Asp Gly Leu Val Cys Leu Leu Lys Lys Pro Phe Asn Arg Pro Gln Gly
            100                 105                 110

Val Gln Pro Lys Thr Gly Pro Phe Glu Asp Leu Lys Glu Asn Leu Ile
        115                 120                 125

Arg Glu Tyr Val Lys Gln Thr Trp Asn Leu Gln Gly Gln Ala Leu Glu
    130                 135                 140

Gln Ala Ile Ile Ser Gln Lys Pro Gln Leu Glu Lys Leu Ile Ala Thr
145                 150                 155                 160

Thr Ala His Glu Lys Met Pro Trp Phe His Gly Lys Ile Ser Arg Glu
                165                 170                 175

Glu Ser Glu Gln Ile Val Leu Ile Gly Ser Lys Thr Asn Gly Lys Phe
            180                 185                 190

Leu Ile Arg Ala Arg Asp Asn Asn Gly Ser Tyr Ala Leu Cys Leu Leu
        195                 200                 205

His Glu Gly Lys Val Leu His Tyr Arg Ile Asp Lys Asp Lys Thr Gly
    210                 215                 220

Lys Leu Ser Ile Pro Glu Gly Lys Lys Phe Asp Thr Leu Trp Gln Leu
225                 230                 235                 240

Val Glu His Tyr Ser Tyr Lys Ala Asp Gly Leu Leu Arg Val Leu Thr
                245                 250                 255

Val Pro Cys Gln Lys Ile Gly Thr Gln Gly Asn Val Asn Phe Gly Gly
            260                 265                 270

Arg Pro Gln Leu Pro Gly Ser His Pro Ala Thr Trp Ser Ala Gly Gly
        275                 280                 285

Ile Ile Ser Arg Ile Lys Ser Tyr Ser Phe Pro Lys Pro Gly His Arg
    290                 295                 300

Lys Ser Ser Pro Ala Gln Gly Asn Arg Gln Glu Ser Thr Val Ser Phe
305                 310                 315                 320

Asn Pro Tyr Glu Pro Glu Leu Ala Pro Trp Ala Ala Asp Lys Gly Pro
                325                 330                 335

Gln Arg Glu Ala Leu Pro Met Asp Thr Glu Val Tyr Glu Ser Pro Tyr
            340                 345                 350

Ala Asp Pro Glu Glu Ile Arg Pro Lys Glu Val Tyr Leu Asp Arg Lys
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         355                 360                 365

Leu Leu Thr Leu Glu Asp Lys Glu Leu Gly Ser Gly Asn Phe Gly Thr
    370                 375                 380

Val Lys Lys Gly Tyr Tyr Gln Met Lys Lys Val Val Lys Thr Val Ala
385                 390                 395                 400

Val Lys Ile Leu Lys Asn Glu Ala Asn Asp Pro Ala Leu Lys Asp Glu
                405                 410                 415

Leu Leu Ala Glu Ala Asn Val Met Gln Gln Leu Asp Asn Pro Tyr Ile
            420                 425                 430

Val Arg Met Ile Gly Ile Cys Glu Ala Glu Ser Trp Met Leu Val Met
        435                 440                 445

Glu Met Ala Glu Leu Gly Pro Leu Asn Lys Tyr Leu Gln Gln Asn Arg
    450                 455                 460

His Val Lys Asp Lys Asn Ile Ile Glu Leu Val His Gln Val Ser Met
465                 470                 475                 480

Gly Met Lys Tyr Leu Glu Glu Ser Asn Phe Val His Arg Asp Leu Ala
                485                 490                 495

Ala Arg Asn Val Leu Leu Val Thr Gln His Tyr Ala Lys Ile Ser Asp
            500                 505                 510

Phe Gly Leu Ser Lys Ala Leu Arg Ala Asp Glu Asn Tyr Tyr Lys Ala
        515                 520                 525

Gln Thr His Gly Lys Trp Pro Val Lys Trp Tyr Ala Pro Glu Cys Ile
    530                 535                 540

Asn Tyr Tyr Lys Phe Ser Ser Lys Ser Asp Val Trp Ser Phe Gly Val
545                 550                 555                 560

Leu Met Trp Glu Ala Phe Ser Tyr Gly Gln Lys Pro Tyr Arg Gly Met
                565                 570                 575

Lys Gly Ser Glu Val Thr Ala Met Leu Glu Lys Gly Glu Arg Met Gly
            580                 585                 590

Cys Pro Ala Gly Cys Pro Arg Glu Met Tyr Asp Leu Met Asn Leu Cys
        595                 600                 605

Trp Thr Tyr Asp Val Glu Asn Arg Pro Gly Phe Ala Ala Val Glu Leu
    610                 615                 620

Arg Leu Arg Asn Tyr Tyr Tyr Asp Val Val Asn
625                 630                 635
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<210> 10
<211> 1108
<212> DNA
<213> Homo sapiens

<400> 10

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35 40 45

Pro Lys Asn Tyr Ile Glu Met Lys Pro His Pro Phe Gly Asn Asp Val
50 55 60

Gln His Phe Lys Val Leu Arg Asp Gly Ala Gly Lys Tyr Phe Leu Trp
65 70 75 80

Val Val Lys Phe Asn Ser Leu Asn Glu Leu Val Asp Tyr His Arg Ser
85 90 95

Thr Ser Val Ser Arg Asn Gln Gln Ile Phe Leu Arg Asp Ile Glu Gln
100 105 110

Val Pro Gln Gln Pro Thr Tyr Val Gln Ala Leu Phe Asp Phe Asp Pro
115 120 125

Gln Glu Asp Gly Glu Leu Gly Phe Arg Arg Gly Asp Phe Ile His Val
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             20                  25                  30

Thr Cys Cys Glu Lys Phe Gly Leu Lys Arg Ser Glu Leu Phe Glu Ala
         35                  40                  45

Phe Asp Leu Phe Asp Val Gln Asp Phe Gly Lys Val Ile Tyr Thr Leu
     50                  55                  60

Ser Ala Leu Ala Trp Thr Pro Ile Ala Gln Asn Arg Gly Ile Met Pro
 65                  70                  75                  80

Phe Pro Thr Glu Glu Glu Ser Val Gly Asp Glu Asp Ile Tyr Ser Gly
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Leu Ser Asp Gln Ile Asp Asp Thr Val Glu Glu Asp Glu Asp Leu Tyr
            100                 105                 110

Asp Cys Val Glu Asn Glu Glu Ala Glu Gly Asp Glu Ile Tyr Glu Asp
        115                 120                 125

Leu Met Arg Ser Glu Pro Val Ser Met Pro Pro Lys Met Thr Glu Tyr
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    130                 135                 140

Asp Lys Arg Cys Cys Cys Leu Arg Glu Ile Gln Gln Thr Glu Glu Lys
145                 150                 155                 160

Tyr Thr Asp Thr Leu Gly Ser Ile Gln Gln His Phe Leu Lys Pro Leu
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Gln Arg Phe Leu Lys Pro Gln Asp Ile Glu Ile Ile Phe Ile Asn Ile
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Glu Asp Leu Leu Arg Val His Thr His Phe Leu Lys Glu Met Lys Glu
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Ala Leu Gly Thr Pro Gly Ala Pro Asn Leu Tyr Gln Val Phe Ile Lys
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Tyr Lys Glu Arg Phe Leu Val Tyr Gly Arg Tyr Cys Ser Gln Val Glu
225                 230                 235                 240

Ser Ala Ser Lys His Leu Asp Arg Val Ala Ala Ala Arg Glu Asp Val
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Gln Met Lys Leu Glu Glu Cys Ser Gln Arg Ala Asn Asn Gly Arg Phe
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Thr Ala Arg Pro Ala Asp Gly Ala Tyr Ala Ala Ser Ser Gln Ile Ser
        275                 280                 285

Pro Pro Ser Pro Gly Ala Gly Glu Thr His Ala Gly Gly Asp Gly Ala
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Arg Lys Leu Arg Leu Ala Leu Asp Ala Met Arg Asp Leu Ala Gln Cys
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Val Asn Glu Val Lys Arg Asp Asn Glu Thr Leu Arg Gln Ile Thr Asn
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Phe Gln Leu Ser Ile Glu Asn Leu Asp Gln Ser Leu Ala His Tyr Gly
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Arg Pro Lys Ile Asp Gly Glu Leu Lys Ile Thr Ser Val Glu Arg Arg
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Ser Lys Met Asp Arg Tyr Ala Phe Leu Leu Asp Lys Ala Leu Leu Ile
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Cys Lys Arg Arg Gly Asp Ser Tyr Asp Leu Lys Asp Phe Val Asn Leu
385                 390                 395                 400

His Ser Phe Gln Val Arg Asp Asp Ser Ser Gly Asp Arg Asp Asn Lys
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Lys Trp Ser His Met Phe Leu Leu Ile Glu Asp Gln Gly Ala Gln Gly
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Tyr Glu Leu Phe Phe Lys Thr Arg Glu Leu Lys Lys Lys Trp Met Glu
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Gln Phe Glu Met Ala Ile Ser Asn Ile Tyr Pro Glu Asn Ala Thr Ala
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Asn Gly His Asp Phe Gln Met Phe Ser Phe Glu Glu Thr Thr Ser Cys
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Lys Ala Cys Gln Met Leu Leu Arg Gly Thr Phe Tyr Gln Gly Tyr Arg
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Cys His Arg Cys Arg Ala Ser Ala His Lys Glu Cys Leu Gly Arg Val
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Pro Pro Cys Gly Arg His Gly Gln Asp Phe Pro Gly Thr Met Lys Lys
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Asp Lys Leu His Arg Arg Ala Gln Asp Lys Lys Arg Asn Glu Leu Gly
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Leu Pro Lys Met Glu Val Phe Gln Glu Tyr Tyr Gly Leu Pro Pro Pro
545                 550                 555                 560

Pro Gly Ala Ile Gly Pro Phe Leu Arg Leu Asn Pro Gly Asp Ile Val
                565                 570                 575

Glu Leu Thr Lys Ala Glu Ala Glu Gln Asn Trp Trp Glu Gly Arg Asn
            580                 585                 590

Thr Ser Thr Asn Glu Ile Gly Trp Phe Pro Cys Asn Arg Val Lys Pro
        595                 600                 605

Tyr Val His Gly Pro Pro Gln Asp Leu Ser Val His Leu Trp Tyr Ala
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Gly Pro Met Glu Arg Ala Gly Ala Glu Ser Ile Leu Ala Asn Arg Ser
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Asp Gly Thr Phe Leu Val Arg Gln Arg Val Lys Asp Ala Ala Glu Phe
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Ala Ile Ser Ile Lys Tyr Asn Val Glu Val Lys His Thr Val Lys Ile
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Met Thr Ala Glu Gly Leu Tyr Arg Ile Thr Glu Lys Lys Ala Phe Arg
        675                 680                 685

Gly Leu Thr Glu Leu Val Glu Phe Tyr Gln Gln Asn Ser Leu Lys Asp
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Cys Phe Lys Ser Leu Asp Thr Thr Leu Gln Phe Pro Phe Lys Glu Pro
705                 710                 715                 720

Glu Lys Arg Thr Ile Ser Arg Pro Ala Val Gly Ser Thr Lys Tyr Phe
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Gly Thr Ala Lys Ala Arg Tyr Asp Phe Cys Ala Arg Asp Arg Ser Glu
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Leu Ser Leu Lys Glu Gly Asp Ile Ile Lys Ile Leu Asn Lys Lys Gly
        755                 760                 765

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<212> DNA
<213> Homo sapiens

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Gly Thr Val Asp Lys Lys Met Val Glu Lys Cys Trp Lys Leu Met Asp
      50                  55                  60

Lys Val Val Arg Leu Cys Gln Asn Pro Lys Leu Ala Leu Lys Asn Ser
 65                  70                  75                  80

Pro Pro Tyr Ile Leu Asp Leu Leu Pro Asp Thr Tyr Gln His Leu Arg
                 85                  90                  95

Thr Ile Leu Ser Arg Tyr Glu Gly Lys Met Glu Thr Leu Gly Glu Asn
            100                 105                 110

Glu Tyr Phe Arg Val Phe Met Glu Asn Leu Met Lys Lys Thr Lys Gln
        115                 120                 125

Thr Ile Ser Leu Phe Lys Glu Gly Lys Glu Arg Met Tyr Glu Glu Asn
    130                 135                 140

Ser Gln Pro Arg Arg Asn Leu Thr Lys Leu Ser Leu Ile Phe Ser His
145                 150                 155                 160

Met Leu Ala Glu Leu Lys Gly Ile Phe Pro Ser Gly Leu Phe Gln Gly
                165                 170                 175

Asp Thr Phe Arg Ile Thr Lys Ala Asp Ala Ala Glu Phe Trp Arg Lys
            180                 185                 190

Ala Phe Gly Glu Lys Thr Ile Val Pro Trp Lys Ser Phe Arg Gln Ala
        195                 200                 205

Leu His Glu Val His Pro Ile Ser Ser Gly Leu Glu Ala Met Ala Leu
    210                 215                 220

Lys Ser Thr Ile Asp Leu Thr Cys Asn Asp Tyr Ile Ser Val Phe Glu
225                 230                 235                 240

Phe Asp Ile Phe Thr Arg Leu Phe Gln Pro Trp Ser Ser Leu Leu Arg
                245                 250                 255

Asn Trp Asn Ser Leu Ala Val Thr His Pro Gly Tyr Met Ala Phe Leu
            260                 265                 270

Thr Tyr Asp Glu Val Lys Ala Arg Leu Gln Lys Phe Ile His Lys Pro
        275                 280                 285

Gly Ser Tyr Ile Phe Arg Leu Ser Cys Thr Arg Leu Gly Gln Trp Ala
    290                 295                 300

Ile Gly Tyr Val Thr Ala Asp Gly Asn Ile Leu Gln Thr Ile Pro His
305                 310                 315                 320

Asn Lys Pro Leu Phe Gln Ala Leu Ile Asp Gly Phe Arg Glu Gly Phe
                325                 330                 335

Tyr Leu Phe Pro Asp Gly Arg Asn Gln Asn Pro Asp Leu Thr Gly Leu
            340                 345                 350

Cys Glu Pro Thr Pro Gln Asp His Ile Lys Val Thr Gln Glu Gln Tyr
        355                 360                 365

Glu Leu Tyr Cys Glu Met Gly Ser Thr Phe Gln Leu Cys Lys Ile Cys
    370                 375                 380

Ala Glu Asn Asp Lys Asp Val Lys Ile Glu Pro Cys Gly His Leu Met
385                 390                 395                 400
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Cys Thr Ser Cys Leu Thr Ser Trp Gln Glu Ser Glu Gly Gln Gly Cys
                405                 410                 415

Pro Phe Cys Arg Cys Glu Ile Lys Gly Thr Glu Pro Ile Val Val Asp
            420                 425                 430

Pro Phe Asp Pro Arg Gly Ser Gly Ser Leu Leu Arg Gln Gly Ala Glu
        435                 440                 445

Gly Ala Pro Ser Pro Asn Tyr Asp Asp Asp Asp Asp Glu Arg Ala Asp
    450                 455                 460

Asp Thr Leu Phe Met Met Lys Glu Leu Ala Gly Ala Lys Val Glu Arg
465                 470                 475                 480

Pro Pro Ser Pro Phe Ser Met Ala Pro Gln Ala Ser Leu Pro Pro Val
                485                 490                 495

Pro Pro Arg Leu Asp Leu Leu Pro Gln Arg Val Cys Val Pro Ser Ser
            500                 505                 510

Ala Ser Ala Leu Gly Thr Ala Ser Lys Ala Ala Ser Gly Ser Leu His
        515                 520                 525

Lys Asp Lys Pro Leu Pro Val Pro Pro Thr Leu Arg Asp Leu Pro Pro
    530                 535                 540

Pro Pro Pro Pro Asp Arg Pro Tyr Ser Val Gly Ala Glu Ser Arg Pro
545                 550                 555                 560

Gln Arg Arg Pro Leu Pro Cys Thr Pro Gly Asp Cys Pro Ser Arg Asp
                565                 570                 575

Lys Leu Pro Pro Val Pro Ser Ser Arg Leu Gly Asp Ser Trp Leu Pro
            580                 585                 590

Arg Pro Ile Pro Lys Val Pro Val Ser Ala Pro Ser Ser Ser Asp Pro
        595                 600                 605

Trp Thr Gly Arg Glu Leu Thr Asn Arg His Ser Leu Pro Phe Ser Leu
    610                 615                 620

Pro Ser Gln Met Glu Pro Arg Pro Asp Val Pro Arg Leu Gly Ser Thr
625                 630                 635                 640

Phe Ser Leu Asp Thr Ser Met Ser Met Asn Ser Ser Pro Leu Val Gly
                645                 650                 655

Pro Glu Cys Asp His Pro Lys Ile Lys Pro Ser Ser Ser Ala Asn Ala
            660                 665                 670

Ile Tyr Ser Leu Ala Ala Arg Pro Leu Pro Val Pro Lys Leu Pro Pro
        675                 680                 685

Gly Glu Gln Cys Glu Gly Glu Glu Asp Thr Glu Tyr Met Thr Pro Ser
    690                 695                 700

Ser Arg Pro Leu Arg Pro Leu Asp Thr Ser Gln Ser Ser Arg Ala Cys
705                 710                 715                 720

Asp Cys Asp Gln Gln Ile Asp Ser Cys Thr Tyr Glu Ala Met Tyr Asn
                725                 730                 735

Ile Gln Ser Gln Ala Pro Ser Ile Thr Glu Ser Ser Thr Phe Gly Glu
            740                 745                 750

Gly Asn Leu Ala Ala Ala His Ala Asn Thr Gly Pro Glu Glu Ser Glu
        755                 760                 765
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Asn Glu Asp Asp Gly Tyr Asp Val Pro Lys Pro Pro Val Pro Ala Val
    770                 775                 780

Leu Ala Arg Arg Thr Leu Ser Asp Ile Ser Asn Ala Ser Ser Ser Phe
785                 790                 795                 800

Gly Trp Leu Ser Leu Asp Gly Asp Pro Thr Thr Asn Val Thr Glu Gly
                805                 810                 815

Ser Gln Val Pro Glu Arg Pro Pro Lys Pro Phe Pro Arg Arg Ile Asn
            820                 825                 830

Ser Glu Arg Lys Ala Gly Ser Cys Gln Gln Gly Ser Gly Pro Ala Ala
        835                 840                 845

Ser Ala Ala Thr Ala Ser Pro Gln Leu Ser Ser Glu Ile Glu Asn Leu
    850                 855                 860

Met Ser Gln Gly Tyr Ser Tyr Gln Asp Ile Gln Lys Ala Leu Val Ile
865                 870                 875                 880

Ala Gln Asn Asn Ile Glu Met Ala Lys Asn Ile Leu Arg Glu Phe Val
                885                 890                 895

Ser Ile Ser Ser Pro Ala His Val Ala Thr
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1999-418926/35 B04 D16 USSH 1997.12.23
US DEPT HEALTH & HUMAN SERVICES *WO 09932627-A2
1997.12.23 1997-068690(+1997US-068690) *(1999.07.01)* C12N 15/12, C07K 14/705, C12N 15/62, G01N 33/50, 33/53, C12Q 1/68, C07K 16/28

Linker for activation of T cell protein used to, e.g. screen for modulators of T cell signaling (Eng)

C1999-123167 N(AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW) R(AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW)

Addnl. Data: SAMELSON L E, ZHANG W
1998.12.23 1998WO-US27400

B(4-C1G, 4-E2F, 4-G1, 4-N2A, 14-A1, 14-C3, 14-G2A, 14-G3, 14-H1) D(5-H9, 5-H11, 5-H12A, 5-H12D2, 5-H17A6) .8

NOVELTY

Isolated polypeptide (I) comprises a part the human LAT (linker for activation of T cells) protein sequence.

DETAILED DESCRIPTION

(I) comprises at least part of the 233 amino acid (aa) sequence (S1) (given in the specification), of the human LAT (linker for activation of T cells) protein.

INDEPENDENT CLAIMS are also included for the following:
(1) a purified antibody (Ab) that binds specifically to (I);
(2) isolated nucleic acid (II) that encodes (S1), or its complement;
(3) method of screening compounds for modulation of interaction between (I) and a LAT-binding ligand;
(4) method for detecting (I) by reaction with Ab; and
(5) method for detecting (II) by hybridization.

ACTIVITY

Immunomodulatory; antimicrobial; anticancer; anti-inflammatory; anti-allergic.

MECHANISM OF ACTION

Modulation of interaction between (I) and the T-cell receptor (TCR) affects the TCR signaling pathway. LAT is a substrate for

tyrosine kinases and becomes phosphorylated after TCR engagement, resulting in recruitment of other signaling molecules.

USE

(I) is used to identify and test (ant)agonists of tyrosine kinase signaling pathways, i.e. modulation of interaction between tyrosine kinase substrates and intracellular ligands or between these ligands and other members of the pathway, including identification of downstream signaling proteins, particularly in immune system cells. These modulators are potentially useful as drugs and diagnostic agents, particularly for diseases that involve undesirable cell growth, differentiation, proliferation or T cell anergy, e.g. neoplasia, inflammation, hypersensitivity/allergy, microbial infection, metabolic, genetic or autoimmune diseases, graft rejection. (I) is also used to generate specific antibodies, used for detection of LAT. Nucleic acid (II) that encodes (I), or its fragments, are used to identify homologous sequences in other species; to detect the LAT gene and as sources of antisense therapeutics.

ADVANTAGE

Modulators of (I) are potentailly more specific and less toxic than known immunosuppressants such as cyclosporin.

ADMINISTRATION

Modulators of (I) are administered parenterally, e.g. at 10-1000 µg/kg.

EXAMPLE

cDNA encoding human LAT (linker for activation of T cells) protein was fused to a myc tag-encoding sequence, then cloned into pcDNA3 for transfection of 293T cells. Immunoblotting with the anti-myc antibody 9E10 indicated presence of a 40 kDa protein in transfected cells only, showing that the cDNA contained the entire coding region.

TECHNOLOGY FOCUS

Biotechnology - Preferred Polypeptides: (I) includes at least one tyrosine residue and is particularly aa 28-233 (the cytosolic domain). (S1) has 10 tyrosine residues in the predicted cytosolic domain and 5 potential binding sites for the Grb2 SH2 domain.
Preferred Nucleic Acid: (S1) is encoded by a 1059 bp sequence (S2) (given in the specification), and this may be part of an expression vector, optionally present inside a host cell.

Preparation: LAT was purified from Jurkat E6.1 cells that had been stimulated with OKT3 ascites, then digested with trypsin and peptide fragments sequenced. The information obtained was used to search the GenBank database and an expressed sequence tag clone (from human fetal heart) identified. A fragment of this clone was used to screen a cDNA library from YT cells and a 1.6 kb fragment identified. It included an open reading frame for (4). LAT mRNA is detected mainly in the thymus and peripheral blood, and at a low level in the spleen. Once isolated, the cDNA can be expressed in vitro or cloned into conventional expression vectors.
Biology - Preferred Methods: In method (3), (I), which can bind a LAT-binding ligand (L); (L) and at least one test compound are incubated together and the extent of (I)-(L) binding measured. Particularly (L) is a tyrosine kinase, specifically ZAP-70 or Syk, and (I) is particularly part of a fusion protein. In method (4), Ab is mono- or poly-clonal and the test sample includes lymphocytes. In method (5), the test material is RNA or DNA, particularly from lymphocytes, and detection of a hybridization complex is correlated with expression of the LAT gene in these cells.
Preparation: Ab are produced by conventional immunization with LAT (or its mutants, fragments) and/or cell fusion methods.
Organic Chemistry - Preparation: Fragments of LAT, and oligonucleotide fragments of (II), are produced by usual methods of chemical synthesis.
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ID AAX89078 standard; DNA; 2758 BP.
XX
AC AAX89078;
XX
DT 14-SEP-1999 (first entry)
XX
DE Nucleotide sequence of human Vav.
XX
KW LAT; tyrosine kinase; linker for activation of T cell; TCR; human;
KW T-cell receptor; TCR signalling pathway; neoplasia; inflammation;
KW hypersensitivity; allergy; microbial infection; genetic disease;
KW autoimmune disease; graft rejection; modulator; Vav; ss.
XX
OS Homo sapiens.
XX
PN WO9932627-A2.
XX
PD 01-JUL-1999.
XX
PF 23-DEC-1998; 98WO-US27400.
XX
PR 23-DEC-1997; 97US-0068690.
XX
PA (USSH) US DEPT HEALTH & HUMAN SERVICES.
XX
PI Samelson LE, Zhang W;
XX
DR WPI; 1999-418926/35.
DR P-PSDB; AAY27125.
XX
PT Linker for activation of T cell protein used to, e.g. screen for
PT modulators of T cell signalling
XX
PS Disclosure; Fig 11A; 125pp; English.

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ID AAY27125 standard; Protein; 797 AA.
XX
AC AAY27125;
XX
DT 14-SEP-1999 (first entry)
XX
DE Amino acid sequence of human Vav.
XX
KW LAT; tyrosine kinase; linker for activation of T cell; TCR; human;
KW T-cell receptor; TCR signalling pathway; neoplasia; inflammation;
KW hypersensitivity; allergy; microbial infection; genetic disease;
KW autoimmune disease; graft rejection; modulator; Vav.
XX
OS Homo sapiens.
XX
PN WO9932627-A2.
XX
PD 01-JUL-1999.
XX
PF 23-DEC-1998; 98WO-US27400.
XX
PR 23-DEC-1997; 97US-0068690.
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PA (USSH) US DEPT HEALTH & HUMAN SERVICES.
XX
PI Samelson LE, Zhang W;
XX
DR WPI; 1999-418926/35.
DR N-PSDB; AAX89078.
XX
PT Linker for activation of T cell protein used to, e.g. screen for
PT modulators of T cell signalling
XX
PS Disclosure; Fig 11B; 125pp; English.
XX
CC The invention relates to a protein tyrosine kinase substrate LAT (linker
CC for activation of T cells) protein. Modulation of interaction between LAT
CC and the T-cell receptor (TCR) affects the TCR signalling pathway. LAT is
CC a substrate for tyrosine kinases and becomes phosphorylated after TCR
CC engagement, resulting in recruitment of other signalling molecules. LAT
CC is used to identify and test (ant)agonists of tyrosine kinase signalling
CC pathways, i.e. modulation of interaction between tyrosine kinase
CC substrates and intracellular ligands or between these ligands and other
CC members of the pathway, including identification of downstream signalling
CC proteins, particularly in immune system cells. These modulators are
CC potentially useful as drugs and diagnostic agents, particularly for
CC diseases that involve undesirable cell proliferation, differentiation,
CC growth or T cell anergy, e.g. neoplasia, inflammation, hypersensitivity/
CC allergy, microbial infection, metabolic, genetic or autoimmune diseases,
CC graft rejection. LAT is also used to generate specific antibodies, used
CC for detection of LAT. Nucleic acid that encodes LAT, or its fragments,
CC are used to identify homologous sequences in other species; to detect the
CC LAT gene and as sources of antisense therapeutics. Modulators of LAT are
CC potentially more specific and less toxic than known immunosuppressants
CC such as cyclosporin. The present sequence represents the amino acid
CC sequence of human Vav.
XX
SQ Sequence 797 AA;
SQ 54 A; 56 R; 29 N; 50 D; 0 B; 21 C; 37 Q; 70 E; 0 Z; 51 G; 16 H;
SQ 38 I; 66 L; 57 K; 18 M; 41 F; 35 P; 44 S; 37 T; 12 W; 32 Y; 33 V;
SQ 0 Others;
mnvsywaiwt renasakrkq flclknirtf lstccekfgl krselfeafd lfdvqdfgkv
iytlsalawt piaqnrgimp fpteeesvgd ediysglsdq iddtveeded lydcveneea
egdeiyedlm rsepvsmppk mteydkrccc lreiqqteek ytdtlgsiqq hflkplqrfl

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